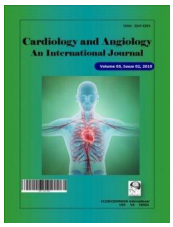

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Hypertension and Uterine Artery Waveform

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Authors' contributions

This work was carried out in collaboration between both authors. Author RJ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author NS managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Pregnancy Induced Hypertension is a multisystem heterogeneous disorder occurring in 4-7% of all pregnancies. Fetal villi in the intervillous space at fetomaternal interphase show ischemic, oxidative and immune mediated damage. This study was conducted to outline the relation between abnormal uterine artery flow and perinatal outcome in a tertiary care center.
Objectives: To assess the relationship between uterine artery Doppler pulsatility index and adverse perinatal outcome.
Materials and Methods: This prospective study involved Doppler ultrasound examination of the uterine arteries at 20-23 weeks gestation in 697 women with singleton pregnancies attending a routine target scan. Pregnancy Induced Hypertension (PIH) was recorded in 57(8.18%) of all pregnancies.
Results: High pulsatility index (>95th percentile) as compared to low pulsatility Index is a good tool for the prediction of PIH (sensitivity 91.23% and specificity 99.06%, $p<0.05$).
Conclusion: Uterine artery Doppler has better detection rates for early onset PIH and Intrauterine Growth Restriction (IUGR). It also has high specificity in the prediction of preterm labor and abruption of placenta.

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Keywords: Hypertension; preeclampsia pregnancy; ultrasonography and uterine artery.

ABBREVIATIONS

HELLP : Hemolysis Elevated Liver enzymes Low Platelet
PIH : Pregnancy Induced Hypertension
IUGR : Intra Uterine Growth Restriction
PI : Pulsatility Index
RI : Resistivity Index
sFLT : soluble FMS Like Tyrosine kinase
sENG : soluble Endoglin
VEGF : Vascular Endothelial Growth Factor
PLGF : Placental Growth Factor
TGF β : Transforming Growth Factor β

1. INTRODUCTION

Preeclampsia can result in eclampsia (Greek word *eklampsis* meaning lightening) or manifest itself as HELLP (Hemolysis, Elevated Liver Enzymes, Low platelet) syndrome. These complications are associated with severe complications like cerebral hemorrhage, lung edema or liver hemorrhage and rupture [1].

Pregnancy has a superadded fetoplacental circulation. The maternal increase in blood volume and cardiac output is 40% after the first 20 weeks of pregnancy [2,3]. These changes will result in severe hypertension in nonpregnant women and yet blood pressure falls in pregnancy. Blood pressure decreases until around 18 weeks of pregnancy and progressively increases towards term [4]. This is possible by a steep reduction in systemic vascular arterial resistance and an increase in venous capacitance. The heart rate increases by 20% to compensate for the drop in systemic vascular resistance [5]. Normal pregnancy therefore has warm skin, prominent veins and orthostatic hypotension.

Two stages of vascular dysfunction exist. In the first stage there is a hemodynamic maladaptation to the increased cardiac output and blood volume in pregnancy and suboptimal development of placenta. This leads to defective placentation. There is acute atherosis and spiral arteries are occluded by fibrinoid material and surrounded by foam cells. Acute atherosis and placental thrombi are also seen in low birth weight babies. The functional changes in placenta are decreased ratio of ProstacyclinI2 to ThromboxaneA2. In preeclampsia there is impaired vasodilator response to endothelium dependent agonists such as acetylcholine and bradykinen. Various adaptive mechanisms are employed at the fetomaternal interphase and subsequently after 20 weeks a clinically evident maternal syndrome of hypertension, edema and proteinuria develops. The development of second stage of late vascular dysfunction can also happen independent of first stage (Fig. 1). The uterine artery Doppler waveform becomes transformed into a high flow with low resistance at 22-24 weeks in normal gestation. However, in preeclampsia there is a latent preclinical stage with impaired intravascular volume expansion, hyper dynamic circulation and a decreased cardiac output as clinical disease develops. This decreased cardiac output leads to renal and uteroplacental insufficiency. There may also be leaky capillaries leading to pulmonary and cerebral edema. Severe and early onset preeclampsia has abnormal uterine artery waveform in preclinical stage and hypertension in clinical stage. Thus, abnormal Doppler of uterine artery may be considered as a local noninvasive imaging of a more generalized systemic vasculopathy. This may mediate further future cardiovascular risks. Women with preeclampsia are also two and a half times likely to die from ischemic heart disease in later life [6,7,8]. This study was conducted to identify the fetomaternal outcome in high PI of uterine artery.

Raised uterine artery impedance is a marker of early endothelial dysfunction. It is associated with increased aortic pulse wave velocity and augmentation index in the first trimester of pregnancy. Increased aortic pulse wave velocity and augmentation index is also a marker of future cardiovascular risk [9,10,11]. Increased homocysteine levels have also been implicated in both cardiovascular risks and preeclampsia [12]. Uterine artery impedance is also associated with adverse perinatal outcome [13,14]. The predominant physiological stimulus for endothelial Nitric Oxide synthesis is flow induced shear stress [15,16]. The clinical presentation of PIH, IUGR, preterm birth and abruption placenta are associated with late endothelial dysfunction. This prospective study was conducted to evaluate the association of increased PI of uterine artery with various disorders of fetomaternal interphase resulting from late endothelial dysfunction in the placental insufficiency.

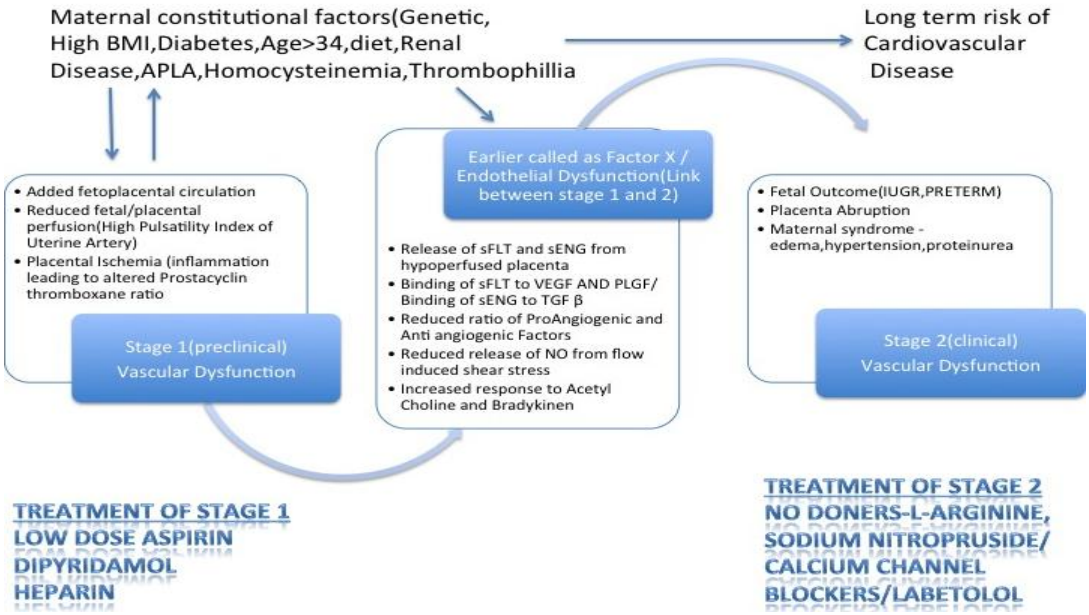

Fig. 1. Conceptual framework of Stage 1 and Stage 2 vascular dysfunction, chronic hypertension and fetomaternal syndrome

2. MATERIALS AND METHODS

This prospective study involved Doppler ultrasound examination of the uterine arteries at 20-23 weeks gestation in women with singleton pregnancies attending a routine target scan. This study was approved by the ethical and research board. All women with no major fetal anomaly were offered the option of uterine artery Doppler evaluation. Written consent was obtained in all cases. A first trimester scan was done to measure Crown Rump Length to date the pregnancy in all cases.

Study was carried out on 697 pregnancies in the Department of Radiology and Department of Obstetrics and Gynecology at Saveetha Medical College and hospital, Chennai, India between 1 April 2015 and 31 December 2016 after getting written informed consent from participants in local language. Multiple Pregnancies and pregnancies with congenital anomalies were excluded. Detailed maternal factors like age, gestational age, parity, pre pregnancy body mass index, previous low birth weight, hemoglobin levels, chronic hypertension, gestational diabetes and previous preeclampsia were recorded. Placental problems like infarcts, retro placental calcifications, small placenta, and premature separation were noted. The ultrasound machines used for the study were PHILIPS HD11XE (Acuson, Mountain View, CA, USA); GE LOGICS7 Expert; Siemens Sonoline Acuson X150 (Siemens).

Pulsed wave Doppler examination of uterine artery in longitudinal scan was used to obtain three similar consecutive waveforms. The same was repeated for the contralateral uterine artery and the mean Pulsatility Index (Maximum-Minimum velocity/Mean velocity) of the two vessels was calculated. Pulsatility Index (PI) rather than Resistivity index (RI) was considered because PI describes the shape of the velocity waveform much better as it includes the area below the curve into the formula. Presence or absence of an early diastolic notch was recorded.125 Hz high pass filter was used to eliminate signals from slowly moving tissues. The curved transducer (3.5-or 5-MHz) had spatial peak temporal average intensities <100 mW/cm^2. Recordings for measurements were obtained in the absence of fetal breathing movement and fetal heart rate between 120 -160 beats per minute. The angle between the ultrasound beam and the direction of blood flow was always less than 50°.

Preeclampsia was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy. This requires two recordings of diastolic blood

pressure of ≥ 90 mmHg at least 4 hour apart in previously normotensive women after 20 weeks of pregnancy, and proteinuria of 300 mg or more in 24 hour, or two readings of at least + + on dipstick analysis of midstream or catheter urine specimens if no 24 hour collection is available. IUGR was defined as fetal weight below the expected weight in the customized population fetal growth charts. Preterm Labor was defined as regular uterine activity before 37 completed weeks of gestation associated with dilatation of cervix. Abruption of placenta was identified as presence of retro placental clots in ultrasound or placental examination after delivery.

3. STATISTICAL ANALYSIS

Mean pulsatility index was not normally distributed and therefore expressed median $\pm$ interquartile range. Fischer exact test was used to analyze maternal history variables. The sensitivity (S), specificity (E), positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio (LR) for a cut off mean PI of 1.55 (95^{th} Percentile) were calculated and bilateral or unilateral notches in the prediction of Pregnancy Induced Hypertension were calculated. Differences were considered significant when $p<0.05$.Logistic regression was used to obtain the Odd's ratio (OR) and 95% CI. Statistical analysis was done using MEDCALC.

4. RESULTS

Doppler examination was done in 750 pregnancies. Satisfactory waveforms were obtained in 743 pregnancies (99%). During the study period, a follow up was available for a total of 697 pregnancies. Uterine artery pulsatility index was not normally distributed but was found skewed to the right with the 95^{th} percentile at 1.55. Table 1 summarizes the maternal history variables associated with PIH.

Table 2 brings up the fact that presence of high pulsatility is a significant risk factor for early onset PIH as compared to late onset PIH. A total of 57 (8.18%) pregnancies resulted in PIH out of total 697 pregnancies. There were no intrauterine deaths. Out of 57 hypertensive pregnancies, 25 were early onset (<34 weeks) and 32 were late onset (>34 weeks).

Gestational age rather than weight was a predictor of neonatal mortality, as all IUGR babies beyond 34 weeks had no neonatal mortality. In 2 neonates (6.25%) no maternal cause of IUGR could be identified. Table 2. brings up the fact that presence of high pulsatility index as compared to low pulsatility confers a significant risk (31.58% v/s 2.19%) for IUGR ($p<0.05$).

It also brings up the fact that presence of high pulsatility as compared to low pulsatility index is a significant risk factor for preterm labor and Abruption Placenta. There were 6 cases of grade one abruption. There were two cases of grade three abruption. There was one case of grade 0 abruption. Out of 32 IUGR newborns, 31 survived beyond four weeks of life.

Table 2 also tells us the sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio positive and likelihood ratio negative of early and late onset PIH, IUGR, preterm birth and abruption placenta when PI>1.55 or there is bilateral or unilateral notch.

5. DISCUSSION

Internal iliac artery is the 3-4 cm division of common iliac artery and the main artery entering the pelvis, whose anterior division gives of the uterine artery (the end artery). While the uterine artery changes from a resistance vessel to a capacitance vessel (fall of RI and PI) the internal iliac artery increases its resistance (RI and PI increase). This is interesting because internal iliac artery is the direct precursor of uterine artery. This ensures that the low resistance uterine artery is rapidly filled by enhanced maternal cardiac output.

Table 1. Screening characteristics of maternal history in pregnancy induced hypertension (PIH). Differences were considered significant when p<0.05.Logistic regression was used to obtain the Odd's ratio (OR) and 95% Confidence Interval (CI)

Characteristic		Odd's ratio	Z statistic	CI	P value
Age	>34	3.3226	2.284	1.1857 to 9.3110	<0.0224
Nulliparity	Yes	2.2612	2.895	1.3015 to 3.9286	<0.0038
Chronic hypertension	Yes	23.8125	5.489	7.6775 to73.8571	<0.0001
Diabetes	Yes	11.8125	5.109	4.5813 to 30.4575	<0.0001

Table 2. Screening characteristics of mean pulsatility index (pi)> 1.55 and/or protodiastolic notch for the prediction of pregnancy induced hypertension (PIH), intrauterine growth restriction (IUGR), preterm labor and Abruptio placenta

Outcome	Sensitivity	Specificity	PPV%	NPV%	LR+	LR-
PIH	91.23	99.06	89.66	99.22	97.31	0.09
PIH<34 Weeks	96.00	94.44	41.38	99.84	18.97	0.04
PIH>34 Weeks	87.50	95.49	48.28	99.37	19.40	0.13
IUGR	59.38	94.14	32.76	97.97	10.12	0.43
IUGR<32 Weeks	87.71	92.46	10.34	99.84	11.37	0.15
IUGR>32 Weeks	52.00	93.30	22.41	98.12	7.77	0.51
Preterm	87.50	95.49	48.28	99.37	19.40	0.13
Abruptio Placenta	66.67	92.44	10.34	99.53	8.82	0.36

Generalized vasodilatation starts during the luteal phase after conception and peripheral resistance falls substantially after 5 weeks gestation, until reaching values 34% lower than the prepregnant state at 20 weeks gestation [17,18]. Arterial pulse wave velocity and augmentation index is consistent with endothelial dysfunction in vivo [19] and in vitro [20] studies. The likely cause is deranged nitric oxide availability, although the precise underlying pathophysiology is unclear. Clinical studies have demonstrated the efficacy of nitric oxide donors to suppress hypertension and improve umbilical cord flow to fetus [21,22]. Ischemic placenta may secrete sFLT (soluble fms like tyrosine kinase) and sENG (soluble endoglin).These decoy molecules trap the available growth factors. The decoy molecule sFLT binds to Vascular Endothelial Growth Factor (VEGF) and Placental Growth factor (PLGF), sENG binds to Transforming growth factor β (TGF β) and thus there is an imbalance of proangiogenic and antiangiogenic factors leading to preeclampsia and fetoplacental complications. The molecule sFLT is a free-floating variant of FLT-1.FLT 1 is a receptor –a docking point of VEGF and PLGF in the vessel wall. This binding process is necessary for vessels to remain healthy. sFLT-1 binds the available VEGF AND PLGF and the vessel walls deprived of VEGF and PLGF remain stiff and inelastic and deteriorate. Endoglin receptor on the vessel wall is a docking point of TGF β. The free circulating levels of sENG act as a decoy diverting TGF β away from vessels. Deprived of TGF β the vessel wall becomes less elastic.

The maternal increase in blood volume and cardiac output is 40% to supply an added fetoplacental circulation. These changes will result in severe hypertension in nonpregnant women but still blood pressure falls in pregnancy. This adaptation to pregnancy is the result of a steep reduction in systemic vascular arterial resistance and an increase in venous capacitance. Normal pregnancy therefore has warm skin, prominent veins and orthostatic hypotension. There is increased flow to skin, kidneys and uterine arteries. Severe and early onset preeclampsia is characterized by hypertension and abnormal uterine artery waveform. Thus, abnormal Doppler of uterine artery may be considered as a local noninvasive imaging of a more generalized systemic vasculopathy. This may be a common factor of cardiovascular risks. The further studies to resolve the maternal cardiovascular maladaptation will involve the echocardiography of maternal heart and mediators of atherosclerosis and oxidative stress in PIH. The plausible explanation of early onset PIH is reduced nitric oxide from vascular endothelium as a result of shear stress that subsequently leads to non-compliant and stiff vessels. High uterine artery pulsatility index is an impaired ability of vasculature to respond to the profound changes required for normal pregnancy [23]. The decreased PI has a protective role and will tend to dampen the increased pulse pressure [24]. This will reduce the transmission of pulsatile energy to the delicate fetal tertiary stem villi floating in the intervillous space. Future research can identify how heparin regulates Vascular Endothelial Growth $Factor_{165}$-dependent

mitogenic activity, tube formation, and receptor phosphorylation in human endothelial cells [25].

6. CONCLUSION

Our study concludes that uterine artery Doppler identifies a subset of pregnant women with a nonresilient cardiovascular system that fails the hemodynamic stress imposed by the superadded fetoplacental circulation. The women manifest as increased peripheral blood pressure, damage of fetal villi and premature separation of placenta. Stage 1 and Stage 2 vascular dysfunction in pregnancy can be useful in identifying future cardiovascular risks. Fig. 1 is a compilation of the conceptual framework representing the understanding of pathophysiology linking high uterine artery pulsatility with future cardio vascular risk and adverse perinatal outcome.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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139

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